Antibiotics and prophylaxis

Drug or Drug Class	*Mechanism of Action*	*Mechanisms of Drug Resistance*
β-Lactams (penicillins, cephalosporins, aztreonam)	Inhibition of bacterial cell wall synthesis	Production of β-lactamase
		Alteration in binding site of penicillin-binding protein
		Changes in cell wall porin size (decreased penetration)
Aminoglycosides	Inhibition of ribosomal protein synthesis	Downregulation of drug uptake into bacteria
		Bacterial production of aminoglycoside-modifying enzymes
Quinolones	Inhibition of bacterial DNA gyrase	Mutation in DNA gyrase-binding site
		Changes in cell wall porin size (decreased penetration)
		Active efflux
Nitrofurantoin	Inhibition of several bacterial enzyme systems	Not fully elucidated—develops slowly with prolonged exposure
Trimethoprim-sulfamethoxazole	Antagonism of bacterial folate metabolism	Draws folate from environment (enterococci)
Vancomycin	Inhibition of bacterial cell wall synthesis (at different point than β-lactams)	Enzymatic alteration of peptidoglycan target

Antimicrobial Agent or Class	*Gram-Positive Pathogens*	*Gram-Negative Pathogens*
Amoxicillin or ampicillin	*Streptococcus*	*Escherichia coli*
	Enterococci	*Proteus mirabilis*
Amoxicillin with clavulanate	*Streptococcus*	*E. coli*
	Enterococci	*P. mirabilis*
		Klebsiella species
Ampicillin with sulbactam	*Staphylococcus* (not MRSA)	*P. mirabilis*
	Enterococci	*Haemophilus influenzae, Klebsiella* species
Antistaphylococcal penicillins	*Streptococcus*	None
	Staphylococcus (not MRSA)	
Antipseudomonal penicillins	*Streptococcus*	Most, including *Pseudomonas aeruginosa*
	Enterococci	
First-generation cephalosporins	*Streptococcus*	*E. coli*
	Staphylococcus (not MRSA)	*P. mirabilis*
		Klebsiella species
Second-generation cephalosporins (cefamandole, cefuroxime, cefaclor)	*Streptococcus*	*E. coli, P. mirabilis*
	Staphylococcus (not MRSA)	*H. influenzae, Klebsiella* species
Second-generation cephalosporins (cefoxitin, cefotetan)	*Streptococcus*	*E. coli, Proteus* species (including indole-positive)
		H. influenzae, Klebsiella species
Third-generation cephalosporins (ceftriaxone)	*Streptococcus*	Most, excluding *P. aeruginosa*
	Staphylococcus (not MRSA)	
Third-generation cephalosporins (ceftazidime)	*Streptococcus*	Most, including *P. aeruginosa*
Aztreonam	None	Most, including *P. aeruginosa*
Aminoglycosides	*Staphylococcus* (urine)	Most, including *P. aeruginosa*
Fluoroquinolones	*Streptococcus* [*]	Most, including *P. aeruginosa*
Nitrofurantoin	*Staphylococcus* (not MRSA)	Many Enterobacteriaceae (not *Providencia, Serratia, Acinetobacter*)

	Enterococci	*Klebsiella* species
Trimethoprim-sulfamethoxazole	*Streptococcus*	Most Enterobacteriaceae (not *P. aeruginosa*)
	Staphylococcus	
Vancomycin	All, including MRSA	None

Penicillins
Bacteriocidal by preventing cell wall formation
Active vs. gram +ve and gram –ve
Pneumonoccal, streptococcus, meningococcus
Benzylpenicillin/penicillin V
Flucloxacillin – Staph aureus
Amp/Amoxicillin hydrophilic: E coli, H Influenzae, Salmonella
Co-amoxiclav: amoxicillin + clavulanic acid
Piperacillin/tazobactam: broad spec inc. Pseudomonas
Side effects
- Rashes and potentially anaphylaxis, occasionally GI upset
- Many people report allergy – need to differentiate between 'true' allergy and side effects

Cephalosporins
Same mode of action as penicillins
Acive vs. gram +ve and gram -ve
1st generation: cefradine, cefalexin more g +ve
2nd generation: cefuroxime 50:50
3rd generation: cefotaxime/ceftraixone more g-ve
ceftazidime also covers Pseudomonas
Think when converting from IV to oral
Cross allergy with penicillins (10%)
Associated with high risk of C.diff

Carbapenems
β-Lactam antibiotic with same mode of action as penicillins
Imipenem/cilastatin (Primaxin), meropenem, ertapenem
Broad spectrum including ESBL producing organisms
Only parenteral route
Caution in epilepsy (cilastin)
Reduce dose in renal failure
Meropenem preferred for MRSA and pseudomonas infection (more difficult to develop resistance compared with Imipenem)
Ertapenem once daily dosing – suitable for outpatient usage
Cross allergy with penicillins 1-10%

Macrolides
Includes erythromycin, clarithromycin, azithromycin
Bacteriostatic /cidal
Inhibit bacterial protein synthesis
Active vs. gram +ve and gram -ve
Similar range to penicillin; additionally mycoplasma, Legionella
Alternative vs. staph and streps
Many significant interactions including statins, cyclosporin, digoxin, antiepileptics, and warfarin (cytochrome p450 oxidase)
Side effects
- Nausea, vomiting, abdominal pain, less commonly rash and urticaria
- Caution in patients with predisposition to prolonged QT interval

Tetracyclines
Includes tetracycline, doxycycline
Bacteriostatic - inhibit bacterial protein synthesis (prolonged Rx required)
Active vs. gram +ve, gram –ve and anaerobes, but increasing resistance
Drug of choice for chlamydia (2 weeks Rx)

Poor absorption (chelate with calcium, iron: avoid co-administration with supplements)
Side effects
- GI disturbance
- Teeth discolouration
- Photosensitivity
- (Avoid in children, pregnancy, breast feeding)

Quinolones
Includes ciprofloxacin, ofloxacin, norfloxacin
Bacteriocidal - inhibits DNA gyrase therefore prevents transcription or replication
Active vs. gram +ve and gram +ve, including pseudomonas aeruginosa, (not Strep. Pneumoniae)
Associated with high risk of C.diff (esp. 027 strain)
Reduced absorption when given with calcium or iron
Well absorbed orally so only IV when not absorbing (IV relatively very expensive)
Side effects
- GI disturbance, headache, rash
- Lowers seizure threshold – caution in epilepsy
- Tendon rupture

Drug interactions
- NSAIDs, theophylline and carbamazepine increase risk of seizures
- Warfarin – INR may increase
- Methotrexate – levels increase, watch for toxicity
- Phenytoin – affects levels and may cause convulsions
- Avoid in children as may cause tendon damage

Trimethoprim
Bacteriostatic - inhibits dihydrofolate reductase (enzyme required for folate production in bacteria)
Active vs. gram+ve and gram-ve, but increasing resistance
1st line for treatment of UTI – reaches high concentrations in the kidney
Well absorbed when administered orally
May accumulate in renal failure – reduce dose after three days if *initial* GFR < 30ml/min
Side effects
- GI disturbance, rashes, hyperkalaemia, blood disorders
- Reduced tubular secretion of creatinine (GFR normal however)

Drug interactions include
- Warfarin – may increase INR – monitor closely
- Methotrexate – reduces MTX excretion so risk of haematological toxicity
- Phenytoin – both have anti-folate effects and increases phenytoin levels
- Digoxin – may increase digoxin levels

Nitrofurantoin
Bacteriocidal, unknown mechanism of action
Poor tissue penetration & low blood levels
Poor activity vs. proteus and klebsiella
Concentrates in urine therefore can be used to treat UTIs
Contra-indicated in mild renal impairment (eGFR < 60ml/min) – does not work
Side effects
- GI disturbances, peripheral neuropathy, hypersensitivity, hepatotoxicity
- Risk of hepatic and pulmonary fibrosis and ocular disturbance almost certainly overstated (few isolated cases reports in literature from > 1 million patient years)

Aminoglycosides
Includes gentamicin, amikacin
Bacteriocidal - inhibit bacterial protein synthesis
Gram-ve mainly, some Gram +ve cocci (staphylococcus)
Synergistic with penicillins as they increase penetration into cell
Highly polar therefore not absorbed orally and do not partition into fat
Dose based on lean body weight – often not performed well (some nomograms use age and height; or ulnar length as surrogate for height)
Side effects

Ototoxicity and nephrotoxicity – monitoring levels is essential

Interactions

Contraindicated in myasthenia gravis – impair neuromuscular transmission
Increased risk of nephrotoxicity when give with ciclosporin
Increased risk of ototoxicity when given with loop diuretics

Glycopeptides

Includes vancomycin and teicoplanin
Bacteriocidal - inhibit cell wall synthesis
Gram+ve organisms (aerobic & anaerobic)
May be used to treat MRSA, Enterococcus
IV route only, exception PO to treat C.difficile
Side effects

Ototoxicity and nephrotoxicity
Levels must be monitored if vancomycin is used (and may be needed for teicoplanin in severe infections)
Vancomycin may cause 'red man syndrome' and hypotension (histamine release) if administered too quickly

Interactions

Increased risk of toxicity when administered with aminoglycosides, loop diuretics or cyclosporin

Nitroimidazoles

Metronidazole
Bacteriocidal - Chemical reduction reaction and inhibits DNA synthesis
Active vs. anaerobes
Diffuses into organism
Alcohol interaction in small proportion of individuals

Rifampicin

Inhibits DNA-dependent RNA polymerase
Always used in combination with other antibiotics
Gram +ve infections, TB, MRSA, C.diff
Use orally as good absorption on empty stomach
Potent liver enzyme inducer so check interactions

Sodium fusidate

Always used in combination with other antibiotics
Good Staph cover
Good penetration to bone & soft tissue
Tablets (fusidate) 500mg tds, syrup (fusidic acid) 750mg tds
Avoid IV route as very irritant & greater risk of liver toxicity

Good prostate penetration

Ciprofloxacin
Doxycycline
Azithromycin/erythromicin
Trimethoprim

Antibiotic prophylaxis

'Antimicrobial therapy administered at or around the time of an invasive procedure in order to reduce infective complications'

Remarkably limited evidence base

Definitions controversial:

- Is urinary tract surgery clean or clean-contaminated?
- Should endpoints be bacteruria or symptomatic UTI/sepsis?

Generally most believe that endoscopic procedures using urethral route 'clean-contaminated' as urethra is colonised; upper tract laparoscopic surgery could be considered 'clean'.

Specific risk factors also influence decision on antibiotic prophylaxis

General risk factors	Special risk factors associated with an increased bacterial load
High age	Long pre-operative hospital stay or recent hospitalization
Deficient nutritional status	History of recurrent genitourinary infections
Impaired immune response	Surgery involving bowel segment
Diabetes mellitus	Colonization with micro-organisms
Smoking	Long-term drainage
Extreme weight	Urinary obstruction
Co-existing infection at a remote site	Urinary stone
Lack of control of risk factors	

Most important:

- Indwelling catheter/stent
- Previous UTI
- Urinary stone disease
- Long pre-operative hospital stay

General considerations:

- Give oral Abx with good bioavailability 1-2hrs pre-op
- Give IV antibiotics at induction
- No randomised data regarding duration of prophylaxis
- No direct recommendations regarding choice of Abx – depends on local sensitivities

<u>Specific procedures</u>

Urethral catheterisation

- Risk of infection low – community 1-2%; hospital 5% men; 10% women
- Risk of associated UTI ~5% per day
- Virtually all patients colonised by 30 days (convenient cut off between short and long-term catheterisation)
- More than one organism typical after 30 days
- Incidence of bacteraemia 4% for routine catheter changes - therefore not indicated routinely (Polastri 1990)

Urodynamics

- Not routine
- Consider for patients with risk factors

TRUS and prostate biopsy

- Good evidence that Abx reduce fever and UTI (Aron 2000)
- At least one day recommended; EAU up to 3 days

BNF recommends single dose oral ciro and metronidazole or single dose IV gent and metronidazole

Cystoscopy

No evidence

TURBT

Little evidence for benefit

Consider in large tumours, prolonged resection time and risk factors

TURP

Majority of evidence supporting prophylactic antibiotics

Meta-analysis by Berry 2002 J Urol

32 studies, n=4260

Bacteriuria 26% to 9.1% with Abx (65% reduction)

Septicaemia 4.4% to 0.7% with Abx (77% reduction)

Any duration of therapy was effective – short course (2-5 days until catheter removed) slightly better than single-dose in reducing bacteriuria (68% vs. 57%).

NB. All patients with significant bacteriuria (without catheter) should have infection eradicated before TURP

BNF recommends single dose oral cipro, IV gent, or IV cefuroxime

ESWL

Overall sepsis seen in ~1% of cases and 3% staghorn calculi

Use of prophylactic antibiotics controversial

2 x RCTs showed no benefit for patients without positive UTI or infection stones. Pearle metaanalysis 2007 however showed reduced UTI rate and reduced hospitalisation in patients receiving prophylactic antibiotics at the time of ESWL (all patients negative MSU pre-Rx)

Current recommendations for prophylactic antibiotics

Infection stones

Positive UTI

History of recurrent UTI

Instrumentation at time of ESWL

Table 8-13 -- Surgical Wound Classification

Clean	Uninfected wound without inflammation or entry into the genital, urinary, or alimentary tract
	Primary wound closure closed drainage
Clean Contaminated	Uninfected wound with controlled entry into the genital, urinary, or alimentary tract
	Primary wound closure closed drainage
Contaminated	Uninfected wound with major break in sterile technique (gross spillage from gastrointestinal tract or nonpurulent inflammation)
	Open fresh accidental wounds
Dirty Infected	Wound with preexisting clinical infection or perforated viscera
	Old traumatic wounds with devitalized tissue

Table 11.4: recommendations for antibiotic prophylaxis in standard urological surgery

Procedure	Pathogens (expected)	Prophylaxis	Antibiotics	Remarks
Diagnostic procedures				
Transrectal biopsy of the prostate	Enterobacteriaceae Anaerobes?	All patients	Fluoroquinolones TMP ± SMX Metronidazole?	Short course (<72h)
Cystoscopy Urodynamic examination	Enterobacteriaceae Enterococci Staphylococci	No	Cephalosporin 2nd generation TMP ± SMX	Consider only in risk patients
Ureteroscopy	Enterobacteriaceae Enterococci Staphylococci	No	Cephalosporin 2nd generation TMP ± SMX	Consider in risk patients
Endourological surgery and ESWL				
ESWL	Enterobacteriaceae Enterococci	No	Cephalosporin 2nd or 3rd generation TMP ± SMX Aminopenicillin/BLI[a]	In patients with stent or nephrostomy tube Consider in risk patients
Ureteroscopy for uncomplicated distal stone	Enterobacteriaceae Enterococci Staphylococci	No	Cephalosporin 2nd or 3rd generation TMP ± SMX Aminopenicillin/BLI Fluoroquinolones	In patients with stent or nephrostomy tube Consider in risk patients
Ureteroscopy of proximal or impacted stone and percutaneous stone extraction	Enterobacteriaceae Enterococci Staphylococci	All patients	Cephalosporin 2nd or 3rd generation TMP ± SMX Aminopenicillin/BLI Fluoroquinolones	Short course Length to be determined Intravenous suggested
TUR of the prostate	Enterobacteriaceae Enterococci	All patients (see Section 10.6.2)	Cephalosporin 2nd or 3rd generation TMP ± SMX Aminopenicillin/BLI	Low-risk patients and small-size prostate require no prophylaxis
TUR of bladder tumour	Enterobacteriaceae Enterococci	No	Cephalosporin 2nd or 3rd generation TMP ± SMX Aminopenicillin/BLI	Consider in risk patients and large necrotic tumours
Open urological surgery				
Clean operations	Skin-related pathogens, e.g. staphylococci Catheter- associated uropathogens	No		Consider in high-risk patients Short post-operative catheter treatment
Clean-contaminated (opening of urinary tract)	Enterobacteriaceae Enterococci Staphylococci	Recommended	Cephalosporin 2nd or 3rd generation TMP + SMX Aminopenicillin/BLI	Single peri-operative course

Clean-contaminated (use of bowel segments)	Enterobacteriaceae Enterococci Anaerobes Skin-related bacteria	All patients	Cephalosporin 2nd or 3rd generation Metronidazole	As for colonic surgery
Implant of prosthetic devices	Skin-related bacteria, e.g. staphylococci	All patients	Cephalosporin 2nd or 3rd generation Penicillin (penicillinase stable)	
Laparoscopic procedures				As for open surgery

Special situations

Risk of endocarditis

NICE guidelines 2008:

At risk patients:

Acquired valvular heart disease (stenosis or regurg)
Valve replacement
Congenital heart disease (including all repairs except ASD, repaired VSD, repaired PDA)
Previous endocarditis
Hypertrophic cardiomyopathy

Antibiotic prophylaxis NOT recommended for patients undergoing genitourinary procedures

For patients undergoing invasive procedures with established GU infection, cover for endocarditis recommended

American Heart Association 1997

Patient Type	*Antimicrobial Recommendation*
High risk	Ampicillin, 2.0 g IM or IV, + gentamicin, 1.5 mg/kg (not to exceed 120 mg) 30 min preoperatively, and ampicillin, 25 mg/kg, or amoxicillin, 25 mg/kg 6 hr postoperatively
High risk with ampicillin or amoxicillin allergy	Vancomycin, 1.0 g over 1-2 hr, + gentamicin, 1.5 mg/kg (not to exceed 120 mg) 30 min preoperatively
Moderate risk	Amoxicillin, 2.0 g 1 hr preoperatively
Moderate risk with ampicillin or amoxicillin allergy	Vancomycin, 1.0 g IV over 1-2 hr, completed ≤ 30 min preoperatively

Vancomycin may be substituted with teicoplanin.

Orthopaedic hardware

AUA/AAOS joint statement 2003:

In general, antimicrobial prophylaxis for urologic patients with total joint replacements, pins, plates, or screws is not indicated. Prophylaxis is advised for individuals at higher risk of seeding a prosthetic joint, including those with recently inserted implants (within 2 years) and/or host risk factors

Patient Type	*Antimicrobial Recommendation*
Total joint inserted > 2 years ago, pins, plates, screws + no host risk factors	Not recommended empirically
Total joint inserted < 2 years ago or aberrant host factor(s)	Oral quinolone or ampicillin, 2 g IV, + gentamicin, 1.5 mg/kg IV, 30-60 min before procedure Substitute vancomycin, 1 g IV, over 1-2 hr before procedure if ampicillin allergy